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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,809	POSSEE ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-34 and 43-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34 and 43-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 April 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 1/5/2004. Claims 1-26 and 35-42 have been canceled. Claims 27 and 43-50 have been amended. Claims 27-34 and 43-50 are pending in this application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Drawings

Figures 3B, 5 last panel and 7 A-C are objected to under 37 CFR 1.83(a) because they fail to show any details as described in the specification. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Figures 3B, Figure 5, last panel, and Figure 7 A-C are photographs of a Northern Blot, Western blot and cell immunofluoresence respectively. The images are dark and no bands or cells are visible. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action filed 12/18/02 and is restated below.**

Applicants claim a genus of *lef1-12, dnapol, pl43, p35, ie-1, p47, ORF1629 and pp31* genes and functional fragments or mutations thereof.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant case, applicants only disclose *lef-2* but do not disclose functional fragments or mutations thereof. The prior art only teaches functional fragments through mutational analysis of the *ie-2* gene. Given the large size and diversity of the Baculovirus family (hundreds of different viruses), the diversity of the recited genes, the absence of disclosed or art recognized correlations between structure and function and the large number of potential fragments and mutations, it must be considered that any functional fragment or mutation must be empirically determined. By disclosing *lef-2*, the applicants have not reduced to practice the claimed invention and the relationship between structure and function is unclear. In an unpredictable art,

the disclosure of one example in one genus would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Response to Arguments-35 USC § 112, first paragraph

Applicants traverse the claim rejections under 35 U.S.C 112, first paragraph, on page 10-11 of the amendment filed 1/5/04. Applicants argue that the one of skill in the art would be able to identify functional fragments or mutations in a matter of routine and not undue experimentation. Applicant further argues that the genes *lef1-12, dnapol, pl43, p35, ie-1, p47, ORF1629 and pp31* are found universally in baculovirus and the assay for functionality is a simple one involving determination that replication is or is not enabled.

Applicant's arguments filed 1/5/04 have been fully considered but they are not persuasive. The skilled artisan cannot envision the detailed structure of the encompassed genes, functional fragments and/or mutations, regardless of the complexity or simplicity of the method of isolation. Applicants recite a large, diverse and highly variant genus of essential Baculovirus genes *lef1-12, dnapol, pl43, p35, ie-1, p47, ORF1629 and pp31* functional fragments or mutations thereof. The single species, *lef-2*, specifically disclosed is not representative of the genus because the genus is highly variant. Neither the prior art nor the specification teaches a correlation between structure and function. The disclosure of a single species does not convey to the skilled artisan that the applicants were in possession of the claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These rejections are maintained for reasons of record in the office action filed 7/1/03 and are restated below.**

Claim 27 recites the step "causing" the recombination of the replication defective baculovirus vector and rescue vector. It is unclear what steps are required to be causative of the recombination.

Claim 29 is unclear for reciting "a gene necessary for restoring the functional gene". It is unclear if this gene is a functional gene required for viral replication or a gene that enzymatically restores the functional gene to its replication competent status.

Response to Arguments- 35 USC § 112, second paragraph

Applicants traverse the claim rejections under 35 U.S.C 112, first paragraph, on page 11-12 of the amendment filed 1/5/04. Applicants state that the rejections under 35 USC 112, second paragraph have been overcome.

Applicant's arguments filed 1/5/04 have been fully considered but they are not persuasive. The claims have not been amended to overcome the rejections under 35 USC 112, second paragraph. Specifically, claim 27 recites the step "causing" and claim 29 "a gene

necessary for restoring the functional gene which have not been amend to more clearly describe the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27-34 and 43-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al (US 6,225,060; see entire document) in view of Patel et al (NAR, Vol 20, pp 97-104; see entire document). **This rejection is maintained for reasons of record in the office action filed 12/18/02 and restated below.**

Applicants claim a method of cloning a gene comprising the steps of providing a replication-deficient baculovirus vector and a "rescue" vector encoding a nucleic acid that restores replication and a transgene. Functional genes are lacking in the baculovirus vector such as *lef* genes and *ie*. The vector is furthermore capable of being maintained in an intermediate host such as yeast or bacteria.

Clark et al teach use of a baculovirus vector for expression of genetic material. Baculovirus vectors comprising transgenes are generated without utilizing cloning steps (see e.g. column 5, line 1-7). As shown in figure two, the method involves the co-transfection of a DNA from a replication deficient baculovirus, deleted of p35 and orf-1629, and a "rescue" vector comprised of baculovirus p35 and orf-1629 genes as well as the transgene. Following co-

transfection into insect cells recombinant baculovirus are selected by screening for replication enablement as a selectable marker (see e.g. column 5, line 1-7 and column 3, line 35-52).

Clark et al do not teach the use of a replication deficient baculovirus vector that can replicate in yeast or bacteria cells as well as insect cells.

Patel et al teaches use of a baculovirus vector that can replicate in Saccharomyces cerevisiae as well as insect cells. A shuttle vector YCbv was generated that could be used to grow in bacteria and yeast and could be used as a recipient of transgene insertion through homologous recombination (see e.g. page 100, column 1, line 1-8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the replication defective baculovirus vector taught by Clark et al with the yeast or bacterial origins of replication taught by Patel et al because Clark et al teach that it is within the ordinary skill of the art to express replication defective baculovirus in a cell and because Patel teach that it is within the ordinary skill of the art to use yeast or bacteria as host cells for recombinant baculovirus vectors. One would have been motivated to do so in order to receive the expected benefit of reducing time consumption (Patel et al, page 97, column 2, third paragraph) and reducing cost due to the lack of need for rounds of plaque purification and the ability to isolate multiple recombinants simultaneously (Patel et al, page 103, column 2, first paragraph). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 27-34 and 43-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitts et al. (Biotechniques, Vol 14 pp 810-817; see entire document) in view of Patel et al. (NAR, Vol 20 pp 97-104; see entire document). **This rejection is maintained for reasons of record in the office action filed 7/1/03 and is restated below.**

Applicants claim a method of cloning a gene comprising the steps of providing a replication-deficient baculovirus vector and a "rescue" vector encoding a nucleic acid that restores replication and a transgene. Functional genes such as *lef*, *ie* and *ORF1629* are removed from the baculovirus vector. The vector is furthermore capable of being maintained in an intermediate host such as yeast or bacteria.

Kitts et al. teach use of a method for producing recombinant Baculovirus in which an essential gene for replication i.e. *ORF1629* is removed or inactivated from the viral genome (see e.g. figure 1). Cells are transfected with a transfer vector (i.e.BacPAK5 and BacPAK6) that contain *ORF1629* linked to a target gene. The baculovirus is rescued following recombination between the genome and BacPAK5 or 6 and thus are replication enabled (see e.g. page 811, column 3, last paragraph). The target gene is then contained in the Baculovirus genome.

Kitts et al do not teach that the replication defective baculovirus vector can be maintained in an intermediate host such as yeast or bacteria.

Patel et al teaches use of a baculovirus vector that can replicate in Saccharomyces cerevisiae as well as insect cells. A shuttle vector YCbv was generated that could be used to grow in bacteria and yeast and could be used as a recipient of transgene insertion through homologous recombination (see e.g. page 100, column 1, line 1-8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the replication defective baculovirus vector taught by Clark et al with the yeast or bacterial origin of replication taught by Patel et al because Clark et al teach that it is within the ordinary skill of the art to express replication defective in a cell and because Patel teach that it is within the ordinary skill of the art to use yeast or bacteria as host cells for recombinant vectors. One would have been motivated to do so in order to receive the expected benefit of reducing time consumption (Patel et al, page 97, column 2, third paragraph) and reducing cost due to the lack of need for rounds of plaque purification and the ability to isolate multiple recombinants simultaneously (Patel et al, page 103, column 2, first paragraph). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 27-34 and 43-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blissard et al (US patent 5,750,383; see entire document) in view of Patel et al (NAR, Vol 20 pp97-104; see entire document). **This rejection is maintained for reasons of record in the office action filed 7/1/03 and is restated below.**

Applicants claim a method of cloning a gene comprising the steps of providing a replication-deficient baculovirus vector and a "rescue" vector encoding a nucleic acid that restores replication and a transgene. Functional genes are lacking the baculovirus vector such as lef genes and *ie*. The vector is furthermore capable of being maintained in an intermediate host such as yeast or bacteria.

Blissard et al. teach use of a novel baculovirus cloning system in which an essential gene for replication, such as the immediate early genes (*ie*), *ie-1* and the *lef* genes (see e.g. column 13, line 15-18), is removed or inactivated from the viral genome. Cells are transfected with a plasmid that contains the essential gene linked to a foreign gene. Thus the baculovirus is rescued and able to propagate normally (see e.g. abstract).

Blissard et al. does not teach that the baculovirus vector can be maintained in an intermediate host such as yeast or bacteria.

Patel et al teaches use of a baculovirus vector that can replicate in Saccharomyces cerevisiae as well as insect cells. A shuttle vector YCbv was generated that could be used to grow in bacteria and yeast and could be used as a recipient of transgene insertion through homologous recombination (see e.g. page 100, column 1, line 1-8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the replication defective baculovirus vector taught by Clark et al with the yeast or bacterial origin of replication taught by Patel et al because Clark et al teach that it is within the ordinary skill of the art to express replication defective in a cell and because Patel teach that it is within the ordinary skill of the art to use yeast or bacteria as host cells for recombinant vectors. One would have been motivated to do so in order to receive the expected benefit of reducing time consumption (Patel et al, page 97, column 2, third paragraph) and reducing cost due to the lack of need for rounds of plaque purification and the ability to isolate multiple recombinants simultaneously (Patel et al, page 103, column 2, first paragraph). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and

absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments- 35 USC § 103

Applicants traverse the claim rejections under 35 U.S.C 103(a) over Clark et al in view of Patel et al on page 5-7 of the amendment filed 1/5/04. Applicants argue that *Trichoplusia ni* must be used to replicate the virus using the system described by Clark therefore creating a stock of virus that is contaminated with non-insert containing and mutation containing vectors. It is argued that the Baculovirus DNA of Patel et al must be recovered from each yeast strain containing the recombinant virus and purified on a sucrose gradient to ensure infectivity. In contrast in the instant invention, the intermediate host of the instant invention is not used to modify the baculovirus but simply for its replication. Finally, applicants argue that there is no teaching, motivation or suggestion to combine Clark et al with Patel et al and once combined, the resultant invention does not represent the present invention as the yeast cells not the insect cells would be used for recombination.

Applicants traverse the claim rejections under 35 U.S.C 103(a) over Kitts et al in view of Patel et al on page 7-8 of the amendment filed 1/5/04. Applicants argue that the virus DNA of Kitts et al must be digested prior to use and as such will leave DNA intact as an infectious circular molecule that can initiate infection in insect cells and produce background virus without foreign gene inserted. The arguments stated above for Patel are repeated to traverse Kitts et al in view of Patel et al.

Applicants traverse the claim rejections under 35 U.S.C 103(a) over Blissard et al in view of Patel et al on page 8-10 of the amendment filed 1/5/04. Applicants argue that Blissard et al uses whole virus particles which infect the cell at different times than the foreign DNA as the replication defective particles eventually replicate after recombination as recombinant virus is made. Therefore, the result of the method of Blissard et al is a heterogenous population of viruses.

Applicant's arguments filed 1/5/04 have been fully considered but they are not persuasive. There is no evidence that the vector of Clark et al results in viral particles that are part of a heterogeneous population or that the vector replicates at low levels in normal insects generating a stock that is contaminated with non-insert containing vectors nor that the vector must be grown in *Tr. ni.* In example 4-example 8, Clark et al utilize Sf9 cells, which are also used in the instant invention. It is not clear that the method of Clark et al requires use of *Tr. ni* cells. Therefore, it would be expected absent evidence to the contrary that baculovirus clones generated according to the method of Clark et al are the same as the baculovirus clones generated by the instant invention.

Patel et al is used as a secondary reference and as such is used only to demonstrate that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the replication defective baculovirus vector taught by Clark et al with the yeast or bacterial origin of replication taught by Patel et al. The modified vector can be **grown** in yeast or bacteria. Clark et al is used as the primary reference and as such teaches the pertinent method steps for the recombination of a baculovirus vector and "rescue" vector for the introduction of transgenes into the recombinant baculovirus.

Motivation to combine Patel et al and Clark et al is found in Patel et al which specifically addresses the need in recombinant technology utilizing baculovirus for a method that is rapid and efficient and ensure that there is no background of parental virus and eliminates the need for time-consuming plaque assays for the production of baculovirus vectors for cloning. The solution according to Patel et al is the propagation of the virus i.e. in yeast (page 103, column 1) which overcomes many difficulties and time-consuming aspects of existing methods. Furthermore, Patel teaches a method of producing Baculovirus clones that is considerably more rapid and efficient than currently used methods and in addition is devoid of any background of parental, non-recombinant virus (page 103, column 2). A person of skill in the art would have been motivated to utilize a baculovirus vector that can be maintained in an intermediate host for rapid and efficient production to ensure that there is no background of parental virus and to eliminate the need for time-consuming plaque assays.

In the method of Kitts et al, there is no evidence that the virus requires multiple screening steps to remove parental contaminants. Furthermore, there is no limitation in the claim that the virus DNA cannot be digested prior to use. Similarly, for Blissard et al, there is no limitation in the instant claims that the instantly recited vector be limited to naked DNA. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). During prosecution, claims must be interpreted as broadly as their terms reasonably allow. Applicants would like to rely on descriptions of the invention that are not reasonably applied to the claims as written.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

April 7, 2004

GERRY LEFFERS
PRIMARY EXAMINER